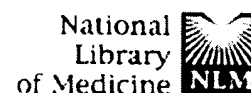


Exhibit 8



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## Identification of a PY motif in the epithelial Na channel subunits as a target sequence for mutations causing channel activation found in Liddle syndrome.

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Liddle syndrome is an autosomal dominant form of hypertension, resulting from mutations in the cytoplasmic C-terminus of either the beta or gamma subunits of the amiloride-sensitive epithelial Na channel (ENaC) which lead to constitutively increased channel activity. Most mutations reported to date result in the elimination of 45-75 normal amino acids from these segments, leaving open the question of the identity of the precise amino acids in which mutation can lead to an enhanced channel activity. To address this question, we have performed a systematic mutagenesis study of the C-termini of the alpha, beta and gamma ENaC subunits of the rat channel and have analyzed their function by expression in *Xenopus* oocytes. The results demonstrate that a short proline-rich segment present in the cytoplasmic C-terminus of each subunit is required for the normal regulation of channel activity. Missense mutations altering a consensus PPPXY sequence of the alpha, beta or gamma subunits reproduced the increase in channel activity found in mutants in which the entire cytoplasmic C-termini are deleted. This proline-rich sequence, referred to as the PY motif, is known to be a site of binding by proteins bearing a WW domain. These findings show that the three PY motifs in the C-termini of ENaC are involved in the regulation of channel activity, probably via protein-protein interactions. This new regulatory mechanism of channel function is critical for the maintenance of normal Na reabsorption in the kidney and of Na<sup>+</sup> balance and blood pressure.

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